Remarks

The Amendments

New claims 29-41 have been added. Support from the claims can be found in *inter alia*, original claims 15, 16, and 28. Additionally, claim 15 has been amended to correct a typographical error. No new matter has been added by these amendments and Applicants respectfully request their entry.

Rejection of Claim 28 Under 35 U.S.C. §102(b)

Claim 28 stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Flemmig *et al.* Applicants respectfully traverse the rejection.

Claim 28 recites a method of detecting the presence of *A. actinomycetemcomitans* (Aa) or an Aa antigen in a test sample. The method comprises contacting a test sample with an antibody or a fragment thereof that specifically binds to a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52, wherein the antibody or fragment thereof specifically binds Aa or an Aa antigen.

Flemmig teaches methods of detecting the presence of Aa antigens in a test sample using outer membrane proteins (OMPs) of ***in vitro* grown** cultures of Aa. The OMPs are used to determine antibody reactivity of human sera to OMPs. Therefore, Flemmig is detecting antibodies in human sera that specifically bind to ***in vitro* grown** OMPs of Aa.

Antibodies or fragments thereof that specifically bind a purified immunogenic polypeptide comprising SEQ ID NO:52 would not specifically bind to *in vitro* grown OMPs of Flemmig because the immunogenic polypeptide of SEQ ID NO:52 is not

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expressed *in vitro*. Since SEQ ID NO:52 is not expressed *in vitro* it would not be present in the *in vitro* grown OMPs of Flemmig.

SEQ ID NO:52 was discovered using IVIAT technology, which identifies polypeptides that are expressed by an organism **only *in vivo***. Therefore, polypeptides that are expressed only *in vitro* or are expressed *in vivo* and *in vitro* (which is different from *in vivo* only) are eliminated from identification by IVIAT. See specification page 9, first and second full paragraphs. That is, IVIAT technology will not identify polypeptides that are produced under *in vitro* conditions or under *in vivo* and *in vitro* conditions. Rather, IVIAT identifies polypeptides that are expressed only under *in vivo* conditions. See specification page 9, first and second full paragraphs. Therefore, IVIAT technology will not identify any *in vitro*-expressed polypeptides. As such, an immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52 and the OMPs of Flemmig are mutually exclusive. One of skill in the art would not expect an *in vivo* only expressed polypeptide identified by IVIAT technology to be among the *in vitro* expressed OMPs of Flemmig. Therefore, SEQ ID NO:52 and fragments thereof would not be present among the ***in vitro*-expressed** OMPs that are used by Flemmig to detect anti-Aa antibodies in human sera. As such, Flemmig cannot anticipate claim 28.

The Office furthermore asserts that Flemmig teaches a method of detecting the presence of an Aa antibody by contacting OMPs from Aa with a test sample. The Office points to the claim language of "immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:52" and asserts that the open-ended term "comprising" fails to exclude unrecited steps or ingredients and leaves the claims open

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for inclusion of unspecified ingredients, even in major amounts. The Office Action concludes that the OMPs of Flemmig read on the claimed immunogenic polypeptides due to the "comprising" language of claim 28.

The OMPs of Flemmig do not read on the recited immunogenic polypeptide **unless** they contain a purified immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:52. The Office Action asserts that the Applicant failed to show Flemmig's OMPs do not contain the claimed immunogenic polypeptide.

However, the examiner bears the burden of presenting at least a *prima facia* case of anticipation. *See In re King*, 231 USPQ 136 at 138-39; *In re Wilder*, 166 USPQ 545, 548 (CCPA 1970). Only if that burden is met, does the burden of going forward shift to the Applicant. *See In re King*, 231 USPQ at 138-139; *In re Wilder,* 166 USPQ at 548. Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987). The Office Action asserts that the disclosed OMPs inherently contain the claimed immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52 because the OMPs were obtained from cell lysates that contain a mixture of polypeptides including an immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52. The Office Action asserts that in the absence of evidence to the contrary, Flemmig reads on the claimed invention since the OMPs bind to specific anti-OMP antibodies. The Office Action concludes that characteristics such as the five contiguous amino acids of SEQ ID NO:52 would be inherent in the preparations of OMP proteins.

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Nothing in Flemmig teaches or suggests that an immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52 would be present in the disclosed OMPs, which were prepared from ***in vitro*** **grown** cultures of Aa. Nor has the Office Action provided anything but a bald assertion that the claimed polypeptide would be present in the preparations of Flemmig.

The fact that a certain characteristic may occur or be present in a prior art reference is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "*In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted); MPEP §2112.01.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP §2112.01. The Office Action has failed to provide this required basis in fact or technical reasoning. Because the Office Action has not demonstrated the presence of an immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:52, the burden remains on the Office to establish a *prima facia* case of anticipation.

Despite the failure of the Office to establish a *prima facia* case of anticipation, the Applicants have indeed shown that an immunogenic polypeptide comprising at least 5

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contiguous amino acids of SEQ ID NO:52 would not be present in the OMPs of Flemmig. While the claims do not recite that SEQ ID NO:52 was obtained using IVIAT technology, the method in which SEQ ID NO:52 was identified is highly relevant. As discussed in Applicants' last response, Flemmig teaches outer membrane proteins of Aa that are isolated from ***in vitro* grown cultures**. See Flemmig, page 678, col. 2., third and fourth full paragraphs. The IVIAT methodology, as explained above, which was used to identify SEQ ID NO:52, specifically removes any antigens that are expressed under *in vitro* growth conditions.

The Office Action asserts that Applicants' arguments regarding the use of IVIAT technology to identify SEQ ID NO:52 is not relevant as the proteins obtained by IVIAT are involved in the pathogenesis of infection. It is true that polypeptides identified by IVIAT technology are involved in pathogenesis of infection; however, more importantly, the polypeptides identified by IVIAT technology are expressed only *in vivo*, that is, only while causing an infection in a susceptible host. The proteins identified by Flemmig may also be involved in pathogenesis of infection; however, these proteins are expressed when Aa is grown *in vitro* (See Flemmig, page 678, col. 2., third and fourth full paragraphs) and are possibly expressed *in vitro* and *in vivo* (which differs from expression *in vivo* only).

Finally, the Office Action asserts that the claims do not recite a method for detecting an antibody that specifically binds to the amino acid sequence of SEQ ID NO:52. Claim 28 recites a method of detecting presence of an Aa antibody in a test sample comprising: contacting a test sample with a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52, wherein the polypeptide

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specifically binds an Aa antibody under conditions that allow formation of an immunocomplex between the antibody and the polypeptide. Therefore, an element of the claim, which must be present in Flemmig for Flemmig to anticipate the claim, is contacting a test sample with a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52. Flemmig does not teach or suggest such a polypeptide and such a polypeptide is not inherently present. Flemmig cannot anticipate claim 28 because it does not teach each and every element of the claims.

Claim 28 is not anticipated by Flemmig and applicants respectfully request withdrawal of the rejection.

Rejection of Claim 28 Under 35 U.S.C. §102(b)

Claim 28 stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ebersole *et al.* Applicants respectfully traverse the rejection.

The Office Action asserts that the use of the open ended term "comprising" in the phrase "immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:52" fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts and thus the polypeptides taught by Ebersole read on the claimed immunogenic polypeptides.

Initially, while other unspecified ingredients may be present, Ebersole must still teach methods using a purified immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:52.

Ebersole teaches the detection of anti-Aa antibodies in test samples by contacting the test sample with ***in vitro* grown** Aa outer membrane antigens (OMAs). Ebersole teaches OMAs of Aa that are isolated from ***in vitro* grown cultures**. See Ebersole, page

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659, second col., first and fourth full paragraphs. In order to anticipate claim 28, Ebersole must teach a method of detecting Aa antibodies using a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52.

Ebersole, however, cannot teach or suggest the claimed polypeptides because Ebersole teaches the use of OMAs that are **expressed *in vitro*** (and possibly expressed both *in vitro* and *in vivo*, which is different from expression only *in vivo*). The polypeptide of SEQ NO:52 was identified using IVIAT methodology and is therefore expressed only *in vivo*. A polypeptide of SEQ ID NO:52 cannot be present in the OMAs used in Ebersole because they are expressed only *in vivo* and would not be present in the ***in vitro* grown cultures** of Ebersole.

Claim 28 is not anticipated by Ebersole and applicants respectfully request withdrawal of the rejection.

Rejection of Claims 15-16 Under 35 U.S.C. §102(b)

Claims 15 and 16 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Snyder *et al.* EP 0439210 (Snyder '210); EP 0439211 (Snyder '211); EP 0439212 (Snyder '212) or Snyder EP 537830 (Snyder '830). Applicants respectfully traverse the rejection.

The Office Action asserts that the Snyder references teach polyclonal antibodies that bind Aa antigens and that can be used to detect the presence of an Aa antigen in a sample. The instant claims recite methods of detecting the presence of Aa or an Aa antigen in a test sample. The methods comprise contacting a test sample with an antibody or a fragment thereof that specifically binds to a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52, wherein the

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antibody or fragment thereof specifically binds Aa or an Aa antigen under conditions that allow formation or an immunocomplex between the antibody and the Aa or the Aa antigen; and detecting an immunocomplex. Detection of the immunocomplex indicates the presence of Aa or an Aa antigen in the test sample.

Therefore, the Snyder references must teach an antibody that binds to a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52 and that can be used to detect Aa or an Aa antigen in a sample. The Snyder references teach that the polyclonal antibodies used in the disclosed methods are generated by injecting rabbits with whole ***in vitro*** **grown** cultures of Aa. See Snyder ('212) page 10, Col. 15, lines 10 through 45; Snyder ('210) page 9, lines 3-49; Snyder ('211) page 3, Col. 3, line 55 through Col. 4, line 24. Therefore, the Snyder antibodies are specific for and bind to Aa antigens that are present in ***in vitro*** **grown cultures** of Aa. In contrast, the claimed antibodies bind SEQ ID NO:52, which is expressed only *in vivo*. The antibodies used in the instant invention are specific for and specifically bind a polypeptide that is **expressed *in vivo* only**, while the antibodies of the Snyder references are specific for and specifically bind polypeptides or antigens that are expressed *in vitro* or expressed *in vivo* and *in vitro* (which is different from expression *in vivo* only). Since a polypeptide of SEQ ID NO:52 is expressed *in vivo* only, it would not have been present in the preparation of *in vitro* grown Aa polypeptides that were used to immunize the rabbits of Snyder. Therefore, the antibodies of Snyder could not specifically bind to a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52 as recited by the instant claims, because a polypeptide of SEQ ID NO:52 was not present in the immunizing composition.

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Claims 15 and 16 are not anticipated by the Snyder references and applicants respectfully request withdrawal of the rejection.

Rejection of Claims 15, 16, and 28 under 35 U.S.C. §112, first paragraph

Claims 15, 16, and 28 stand rejected as lacking enablement under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection.

The Office Action asserts that "a purified immunogenic polypeptide comprising at least 5 contiguous amino acids of SEQ ID NO:52" is not enabled by the specification. The Office Action asserts that it is not clear fragments of SEQ ID NO:52 can be predictably modified and which regions are critical and what variants, if any can be made that retain the [biological activity], without undue experimentation.

First, the Office Action has not presented a *prima facia* case of lack of enablement. When rejecting a claim under the enablement requirement of §112 the Patent Office bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification. This includes providing sufficient reasons for doubting assertions. See MPEP §2164.04; *In re Wright*, 27 U.S.P.Q.2d 1510,1513 (Fed. Cir. 1993). "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and reasoning which is inconsistent with the contested statement." See MPEP §2164.04; *In re Marzocchi*, 169 U.S.P.Q.367, 370 (CCPA 1971).

The Office Action has not provided sufficient reasons for doubting the enablement of the use of antibody fragments or fragments of SEQ ID NO:52 other than

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stating that the declaration of record and specification do not disclose fragments of antibodies or fragments of SEQ ID NO:52 that have been used in the instant methods. However, the specification does indeed provide this disclosure. *See e.g.,* page 21, lines 7-10; page 11, lines 13-15; page 14, lines 6-21.

Applicants remind the Office that the Office must accept at being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence to question them.

Second, despite the failure of the Office Action to establish a *prima facia* case of enablement, the claims are indeed enabled. Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, the specification must teach one skilled in the art how to make and use fragments of antibodies or fragments of SEQ ID NO:52. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. "The determination of what constitutes undue experimentation is a given case requires the application of a standard of reasonableness, having due regard of the nature of the invention and the state of the art." *In re Wa*nds, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Ansul Co. v. Uniroyal, Inc.*, 169 U.S.P.Q. 759, 762-63 (2d Cir. 1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable

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amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*

A fragment of 5 or more contiguous amino acids of SEQ ID NO:52 can easily be made by one of skill in the art. *See e.g.*, specification at page 16, line 1-11. The fragment can be tested for activity using only routine methods, for example an ELISA assay. *See e.g.*, page 15, lines 14-19.

Additionally, the Office Action asserts that fragments of antibodies that specifically bind a polypeptide of the invention are not enabled. If an antibody that specifically binds to SEQ ID NO:52 is enabled, then fragments of antibodies are enabled. The specification teaches that:

> Fragments of antibodies are a portion of an intact antibody comprising the antigen binding site or variable region of an intact antibody, wherein the portion is free of the constant heavy chain domains of the Fc region of the intact antibody. Examples of antibody fragments include Fab, Fab', Fab'-SH, $F(ab')_2$ and F_v fragments. See page 20, lines 7-10.

One of skill in the art could certain make and use the claimed antibody fragments because antibody fragments are well known in the art. Methods of making and using antibody fragments are also well known to one of skill in the art.

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Therefore, claims 15, 16, and 28 are enabled and Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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